The metabolic syndrome in an Italian psychiatric sample: a retrospective chart review of inpatients treated with antipsychotics

La sindrome metabolica in un campione italiano di pazienti psichiatrici: uno studio retrospettivo su soggetti trattati con antipsicotici

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SUMMARY. Introduction. The metabolic syndrome (MS) is an area of interest for mental health research because individuals with mental illnesses have an increased risk of medical morbidity and mortality compared with the general population. This cross-sectional study is aimed to estimate the prevalence of metabolic syndrome in an Italian psychiatric sample, treated with different types of antipsychotics. **Methods.** The data were derived from medical records of patient with affective and non-affective psychosis, admitted to the Hospital of L'Aquila psychiatric ward, from January 2012 to July 2014. The sample refers to consecutive admissions of subjects of both sexes, aged over 18 years, receiving one or more antipsychotic treatment. The diagnosis of MS was established when the clinical subject at least three of the five diagnostic criteria of the Adult Treatment Panel (NCEP-ATP III) were met. **Results.** 389 subjects were evaluated. We report a MS prevalence of 27.5%. This figure is very close to the metabolic syndrome prevalence in the Italian general population quoted around 26%. The BMI values also are very similar in these two populations, despite a higher obesity rate in the clinical sample. The MS prevalence rates in subject with schizophrenia, bipolar disorders and depressive disorders were respectively 30.6%, 36.4% and 36.8%. No significant differences in MS, diabetes or dyslipidemia rates were found among the three diagnostic groups. We did not find differences in metabolic syndrome prevalence either in relation to psychotropic polypharmacy or in relation to typical or atypical antipsychotics. However the psychiatric females in the clinical sample tend to have higher obesity rate, with a sort of all or none distribution (i.e. more obesity, more normal weight, but less overweight) compared to the general population. **Conclusions.** These findings could be explained by the interaction of some sort of liability due to drug treatment, illness related lifestyles, gender and other interacting factors (e.g. genetic) with metabolic issues.

KEY WORDS: schizophrenia, bipolar disorder, depressive disorders, metabolic syndrome, overweight, obesity.

RIASSUNTO. Introduzione. La sindrome metabolica (SM) è un tema di interesse centrale nell'ambito della salute mentale, visto l'aumentato rischio di comorbilità medica e di mortalità tra gli individui con patologia psichiatrica grave rispetto alla popolazione generale. Il presente studio trasversale è volto a stimare la prevalenza della SM in un campione di pazienti psichiatrici di nazionalità italiana, trattati con diversi tipi di antipsicotici. **Metodi.** I dati sono stati raccolti da cartelle cliniche di pazienti con psicosi affettive e non affettive, ricoverati consecutivamente presso il reparto psichiatrico dell'ospedale dell'Aquila, dal gennaio 2012 al luglio 2014. Il campione si riferisce a individui di entrambi i sessi e di età superiore ai 18 anni, in trattamento con uno o più antipsicotici. La diagnosi di SM è stata formulata in accordo ai criteri diagnostici del Treatment Panel (NCEP-ATP III). **Risultati.** Sono stati valutati 389 soggetti. Il 27,5% del campione risulta affetto da SM, prevalenza molto simile a quella riportata per la popolazione generale italiana che si attesta intorno al 26%. Allo stesso modo, i valori di BMI risultano essere molto simili tra queste due popolazioni, mentre, nel campione clinico, si registra un tasso di obesità più elevato. I tassi di prevalenza di SM nei sottocampioni di pazienti affetti da schizofrenia, disturbi bipolari e disturbi depressivi sono stati rispettivamente 30,6%, 36,4% e 36,8%. Fra i tre gruppi diagnostici non si evidenziano differenze significative nella prevalenza della SM, il diabete o la dislipidemia. Non emergono differenze significative nella prevalenza della SM né in relazione alla politerapia antipsicotica, né in relazione all'utilizzo di antipsicotici tipici o atipici. Nell'ambito del campione clinico, si registrano, tuttavia, tassi di obesità più elevata per i soggetti di sesso femminile, con una distribuzione del tipo "Tutto o nulla" (cioè maggiori tassi di obesità e normopeso, minori tassi di sovrappeso) rispetto alla popolazione generale. **Conclusioni.** I risultati del nostro studio potrebbero essere spiegati con l'interazione di più fattori quali il trattamento farmacologico, i lifestyle malattia correlati, il sesso e altre variabili (per es., predisposizione genetica) che concorrono a determinare problematiche metaboliche di diversa natura.

PAROLE CHIAVE: schizofrenia, disturbo bipolare, disturbo depressivo, sindrome metabolica, sovrappeso, obesità.

INTRODUCTION

The metabolic syndrome (MS), also called Dismetabolic Syndrome or Syndrome X, has been discussed in cardiology and endocrinology for over two decades, but the last five years have seen an explosion of publications in this area[1,2].

The MS is defined by a cluster of several risk factors that include increased abdominal or visceral adiposity, measured

by waist circumference, atherogenic dyslipidemia (i.e. low HDL and elevated fasted triglycerides), hypertension, and impaired fasting glucose or overt diabetes mellitus[3]. The National Cholesterol Education Program (NCEP) definition is commonly used, although recent Consensus Panels [National Heart, Lung and Blood Institute and American Heart Association (AHA)] suggest that the new lower threshold for impaired fasting glucose of 100 mg/dl be added[4]. In the United States increased attention to MS followed the NCEP publication of its third Adult Treatment Protocol (ATP-III) in 2001[3]. By highlighting the MS as a condition worthy of clinical attention due to its association with increased cardiovascular (CV) risk, and providing clinicians with easily verifiable clinical criteria, ATP-III facilitated and made identification of persons with the syndrome easier[5].

The concept of MS has several practical uses. A main point is the everyday clinical check of patients, to identify those at higher risk for cardiovascular diseases (CVD) or type 2 diabetes (MD2). In the last decades about 10,000 reviews were published about MS. At first, efforts were directed to produce guidelines for the general population in primary care setting. More recently, special attention has been focused on clinical populations or some specific populations, such as the pediatric or geriatric ones[6-8].

Among others, the mental health has represented an area of interest for metabolic syndrome research[9]. Individuals with mental illnesses have a dramatically increased risk of medical morbidity and mortality as compared to the general population. CV-related deaths alone are more than twice as common in the mentally ill population, as compared with non-mentally ill individuals. Patient with schizophrenia suffer from a spectrum of somatic disorders similar to the general population one, but they die at a younger age[10].

It has been reported that individuals with serious mental disorders (SMDs) have a shorter life expectancy, particularly because of an increased suicide rate, but also due to the increased risk of CV diseases, among others[11].

The mortality due to CV diseases is doubled in patients with schizophrenia. The reason is partly to be found in the increased prevalence of general CV risk factors in this population, such as obesity, hyperglycemia, hypertension, dyslipidemia and smoking[12]. In addition, daily living habits and lifestyles may contribute to increase the CV risk factors (i. e. smoking, lack of physical exercise or inadequate eating habits)[11].

Long-term treatment with antipsychotic drugs in patients with schizophrenia is essential for the proper management of symptoms and to improve their prognosis. The ATPs are very heterogeneous in terms of both clinical efficacy and safety[13]. The introduction of the atypical ATPs represented a change in the tolerability profile of antipsychotics, reducing the appearance of extrapyramidal effects and tardive dyskinesia, but also facilitating the development of alterations associated with metabolic and/or CV risk, also in drug naive patients[14,15]. In recent years a growing interest has focused on the study of the physical comorbidities associated with psychiatric disorders and the use of ATPs[11]. Most of these studies have focused on the analysis of the prevalence of obesity, cardiovascular risk, diabetes mellitus or metabolic syndrome in schizophrenia[16-18] and, to a lesser degree, in bipolar disorder[19-21].

Clozapine and olanzapine, followed by quetiapine and risperidone are associated with the greatest weight gain and the highest occurrences of diabetes and dyslipidemia. Little or no significant weight gain, diabetes or dyslipidemia have been seen with aripiprazole and ziprasidone; however, the long-term data for these drugs are limited[22]. The CATIE clinical trial, which included schizophrenic patients receiving antipsychotic treatment, found that MS prevalence was 40.9%, using the NCEP criteria. In females it was 51.6%, compared to 36% (p=.0002), for males[5].

Because of the different impact of demographic features and life styles on both MS and psychosis, and the relatively lack of national data on a large epidemiological sample, we were aimed to report data on an inpatient large Italian psychiatric sample treated with different types of antipsychotics.

METHODS

A cross-sectional analysis was based on the administrative database records of adult inpatients managed under routine clinical practice condition. The analysis was done on chart review collected in the last 30 months in the Psychiatric Unit of San Salvatore Hospital in L'Aquila. The sample refers to consecutive admissions of both sexes, aged over 18 years, with the diagnosis of affective and non affective psychosis (bipolar disorder, major depressive disorder, schizophrenic and schizophreniform disorders, schizoaffective disorder), receiving one or more antipsychotic treatment.

The documented clinical parameters comprised the following: body mass index (BMI, kg/m2), systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg), baseline blood glucose (mg/dl), triglycerides (mg/dl), total cholesterol (mg/dl), low density lipoprotein (LDL) cholesterol (LDL-cholesterol, mg/dl), and high density lipoprotein (HDL) cholesterol (HDL-cholesterol, mg/dl) and prolactin (ng/ml). Furthermore weight, height, and smoke habit were collected. The data were obtained on a computerized basis, with due observation of the legal regulations on information confidentiality.

The diagnosis of MS was established when the clinical subject was found to meet three of the following five diagnostic criteria of the Adult Treatment Panel (NCEP-ATP III): (a) serum triglycerides ≥150 mg/dl or treatment with triglyceride-lowering drugs; (b) HDL-cholesterol <40 mg/dl in males or <50 mg/dl in females; (c) systolic/diastolic blood pressure ≥130/85 mmHg or subjected to antihypertensive treatment; (d) fasting blood glucose ≥110 mg/dl, or subjected to glucose-lowering treatment with oral antidiabetics, or previously diagnosed diabetes mellitus; and/or (e) waist circumference ≥102 cm in males or ≥88 cm in females.

To compare the data of our psychiatric sample with those of the Italian general population, we referred to a study conducted by The Italian Epidemiological Cardiovascular Observatory[23].

The statistical analysis consisted initially of descriptive measures for the variables under study. For this purpose, frequencies and percentages were used for categorical variables and means, medians and standard deviations were used for quantitative variables.

The Multivariate Analysis of Variance (MANOVA) was used to compare three dataset (gender, diagnosis and pharmacological treatment), to investigate differences in metabolic parameters. The chi-square test was used to evaluate the difference in prevalence between the genders.

The z test two proportion was used to compare the metabolic risk factors percentage of the clinical sample and the general population. In all the statistical tests used, differences were considered to be significant when p was less than 0.05. The analyses were performed with the software SPSS 19,0 (IBM Corp, Armonk, NY).

RESULTS

The reference group was composed of 389 subjects (50.4% males). The mean age of the subjects was 46.87±15.56 years. 42.6% of these patients were diagnosed with affective disorder, whereas the remaining 57.4% were diagnosed with psychotic spectrum disorder. The majority of subjects was treated with only one antipsychotic (64%). 55.8% of this group received a second generation antipsychotic, 44.2% a first generation antipsychotic. The remaining 36% were treated with a combination of two or more antipsychotics: 57.9% of these combined a first- with a second-generation agent, 18.6% combined 2 second-generation drugs and 23.6% combined 2 first-generation antipsychotics.

The prevalence rates of MS according to the ATPIII criteria in our sample were 27.5%. The presence of the specific criteria are shown in Table 1.

Metabolic parameters as depended variables were examined for male vs female, antipsychotics treatment, and diagnosis (schizophrenic disorders, depressive disorders and bipolar disorders) by multivariate test (Table 2). Wilk's Lambda for diagnosis .96 and antipsychotics treatment .95 did not statistical differ. Gender factor had a statistical significance (Wilk's Lambda 0.92, F=4.49; p=0.000). No statistical interaction were seen.

When gender difference for Panel III variables were examined with chi square analysis using above and below threshold, waist difference only differed between two groups, with values higher in female (χ^2=7.6; p=0.007).

When the sample was divided by ICD diagnosis, the MS prevalence rates in non-affective psychosis, bipolar disorder and depressive disorder were respectively 30.6%, 36.4% and 36.8%. No differences in MS, diabetes or dyslipidemia rates were found among the three diagnostic groups. Since there were no differences in metabolic aspects between affective and non-affective disorders, in the subsequent analysis the sample was considered collapsed.

When splitting the sample into two groups based on single vs multiple antipsychotic agents, we found significant differences in the total cholesterol, higher in multiple pharmacotherapy (188.7±45.2 vs 176.05±43.4; p=0.009) and in HDL cholesterol, higher in single pharmacotherapy (44.5±12.5 vs 40.0±11.1; p=0.001).

Table 3 reports the descriptive statistics of each metabolic risk factors rate found in our study population. This table also shows the observed values for the same parameters in the general Italian population (i.e. men and women between 35 and 79 years), obtained from a study conducted by the Italian Cardiovascular Epidemiological Observatory between 2008 and 2010[23]. Using the two proportion z test to compare clinical and general population, statistically significant differences between the rates of metabolic factors were found. The percentages of diabetes and MS were statistically different for the two samples females (respectively z=3.54, p<0.0005; z=2.37, p<0.025). Therefore, as shown in Table 3, significant differences in obesity and overweight for both sexes were observed, while the percentage of normal weight was statistically different for two population male (z=1.73, p<0.10).

DISCUSSION

To our knowledge, this is the first Italian study that specifically assesses the prevalence of MS in patients with mental

Table 1. Metabolic syndrome and prevalence criteria in among all subjects

Criteria	All
MS	27.5%
Waist (M>102; F>88)	47.4%
Blood pressure (≥130/85)	16.6%
HDL (M<40; F<50)	61.9%
Glucose (≥110)	16.8%
Triglyceride (≥150)	30.8%

Table 2. Metabolic risk factors stratified by gender and antipsychotic treatment

Metabolic parameters	Male (n=193)			Female (n=196)		
	Antipsychotic treatment			Antipsychotic treatment		
	First generation antipsychotics (n=40)	Second generation antipsychotics (n=65)	Combined antipsychotics (n=45)	First generation antipsychotics (n=69)	Second generation antipsychotics (n=73)	Combined antipsychotics (n=33)
Waist circumference	96.35+13.96	100.52+13.56	102.93+15.40	93.54+20.02	92.02+17.46	86.50+18.04
Systolic blood pression	127.87+13.91	124.77+11.51	130.33+13.91	124.86+15.76	124.45+14.73	123.79+12.31
Dyastolic blood pression	79.25+5.7	79.15+8.08	81.33+8.56	78.04+9.32	78.15+7.93	78.49+7.23
HDL cholesterol	36.95+10.48	39.51 +10.68	35.42+8.45	48.07+11.51	47.08+13.07	43.39+10.92
Glycemia	81.85+11.39	88.08+28.68	86.58+31.40	83.55+13.20	91.96+38.78	91.12+38.21
Tryclicerides	136.60+81.16	161.72+93.78	142.09+70.00	131.96+99.31	133.10+99.61	121.79+64.91

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Table 3. Descriptive statistics of each metabolic parameter				
	Psychiatric sample		General population	
Risk Factors	Men (n=196)	Female (n=193)	Men (n=1924)	Female (n=1926)
Diabetes (%)	15.4 [a]	18.3 [b]	15.2	10.0
MS (%)	24.4 [c]	30.5 [d]	29.0	22.9
BMI (Kg/m^2)	27.0±5.2	27.5±6.8	27.8±4.5	27.4±8.3

BMI cat (%)
  Obesity
  Overweight
  Normal weight
	32.8 [e]
	41.8 [g]
	25.4 [i]
		32.7 [f]
		24.6 [h]
		42.7 [l]
			25.0
			48.1
			26.8
				26.6
				33.8
				39.5

Hypercolesterolemia (%)	26.8	38.9	45.6	52.2
High blood pressure (%)	17.1	16.1	36.5	31.0
Smoke habits (%)	62.8	40.4	22.4	19.9

z-test for two proportion comparison: Diabetes: [a] z=.07, NS; [b] z=3.54, p<.0005
MS: [c] z=1.36, NS; [d] z=2.37, p<.05
BMI categories: Obesity [e] z=2.38, p<.05; [f] z=1.81, p=.06; Overweight [g] z=1.68, NS; [h] z=2.59, p<.01; Normal weight [i] z=.42, NS; [l] z=.86, NS

disorders. Considering that the prevalence rates in Italian general population is 26%[23], the prevalence of MS found in this study (27.5%) is only slightly higher than that of the general population.

The multivariate ANOVA on metabolic parameters as depended variables did not showed differences for antipsychotics treatment and diagnosis but differences between sexes emerged. Although waist circumference showed a gender differences, being lower among female, when values above threshold for both sexes were considered, females exceeded the male counterpart.

As shown in Table 2, this difference is mainly due to the higher MS prevalence rate in psychiatric females, which also have higher levels of diabetes, compared to the general population[23]. The BMI values are very similar in these two populations, despite a higher obesity rate in the clinical sample, with a sort of all or none distribution (i.e. more obesity, more normal weight, but less overweight). These findings could be explained by the interaction of some sort of liability due to drug treatment, illness related lifestyles of other interacting factors (e.g. genetic)[24] with metabolic issues able to push the distribution of normal, overweight and obesity categories toward the two extremes values.

Surprisingly, some parameters of metabolic risk such as hypertension and hypercholesterolemia in the general population are higher than those in our sample. This result could be explained by mean age difference in two samples that was about 10 years lower in our clinical sample. This indeed includes individuals between 18 and 35 years, who have been left out in the general population sample. The CATIE clinical trial, which included patients receiving antipsychotic treatment matched for age, race, and gender with subjects from the NHANES study[5,25-27], estimated the mean risk of serious fatal and nonfatal Coronary Heart Disease (CHD) within 10 years, according to the Framingham function, at 9.4% in males and 6.3% in females[26]. It is also possible that the use of some antipsychotic drugs, which include hypotension among their side effects, may has played a greater role in down regulating blood pressure greater than the general population.

Furthermore, in clinical sample unhealthy lifestyles, such as smoking habit, were more represented than in general population. Indeed smoking habit, a key factor for a significantly shorter life expectancy, results two to three times higher (Table 2), confirming literature results of people with mental illness have a higher incidence of smoking-related diseases[28-30].

The female gender is significantly associated with a higher prevalence of MS in our study (female 30.5% vs male 24.4%). This result is in accordance with several psychiatric studies that compared the rates between gender, most of them revealing substantially increased prevalence rates of MS in women[31], up to three times when compared to those in men[32]. These results are suggestive of a potential sex-specific vulnerability to this disease and/or to metabolic effects induced by psychotropic drugs[33]. We found no differences in metabolic parameters between diagnoses.

The prevalence of MS in our patients with schizophrenia (30.6%) was lower than the value between 42.4% and 62.5% found in North America[34,35], and the value of 34.6% and 37.1% found in Sweden[36] and Finland[37].

In our sample the MS prevalence found in bipolar patients was in line with data from literature (36.4%).The literature shows a MS prevalence between 16.7% and 50%[11,19,20,38,39]. The studies related to the depression found the prevalence of MS relatively discordant. The majority of works was performed on outpatients and reported prevalence between 10%[40] and 36%[41]. Another study carried out on inpatient of a psychiatric ward of a general hospital in Brazil found a prevalence of 48.1% for depression[42]. In our study the prevalence found was a bit lower (26.8%), considering the condition of hospitalization of patients evaluated.

Even though no difference was found in MS rate between single vs multiple pharmacotherapy, it seems possible that the patients treated with more antipsychotics have a worse metabolic panel than those treated with one single drug. Although some studies have found that a polypharmacy with antipsychotic drugs, compared to a monotherapy with one drug, does not increase the prevalence of MS[43-45], our obser-

vation that antipsychotic polypharmacy is associated with an increased risk of metabolic syndrome is consistent with the results of several other studies[37,46].

With regard to the differential risk of conventional and typical antipsychotic for MS, the result of the present study did not show differences between the two classes of compounds. Most other studies, however, demonstrated that MS-components are more often present in patients treated with atypical antipsychotics[47,48], and this effect is most probably related to their receptor binding profile[49,50].

Recent pharmacogenetic studies demonstrate that the different drugs response in terms of efficacy and of side effects is the result of pharmacokinetic and pharmacodynamic processes that can be influenced in part by genetic mechanisms. This could explain that individuals exposed to the same class of drugs show significant inter-individual differences with regard to the metabolic type side effects[51].

As a retrospective study, this has a limit since current psychotropic medication was recorded, but the possible metabolic effect of any prior treatment was not considered. Furthermore, the cross-sectional nature of this study is not suitable to determine the exact duration of psychotropic treatment prescribed in the previous years. In addition to possible effects due to medications, other factors may be involved in the MS onset, such as biological vulnerability associated with the mental disorder itself[52,53], and additional risk factors such as lack of physical activity and unbalanced diet[54]. As these factors were not evaluated in this study, it cannot be excluded a priori that they have influenced the results.

The present study shows that the metabolic alterations in patients with severe mental illness are almost similar to those found in other European countries, although with lower rates of metabolic syndrome prevalence. We could hypothesize that these differences in prevalence may be due to different lifestyles and eating habits, and that the Italian diet could be represent a protective factor. The adherence to an overall food pattern in line with the Mediterranean Diet has been demonstrated to significantly reduce the prevalence of metabolic syndrome[55].

The findings suggest that clinicians should carry out regular checks on physical health to detect the possible metabolic syndrome presence, regardless of the antipsychotic type prescribed. Clinicians should also ensure that patients with identified physical comorbidities receive medical care readily and increase the focus of clinical interventions through strategies to promote physical well-being.

Conflict of interests: the authors declare they have no competing interests.

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